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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009687

AUG 19 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Harmony® Extra Herbicide - Response to TB II Questions Re: Tolerance Petitions for Thifensulfuron Methyl and Tribenuron Methyl on Oat Grain and Straw

TO: Joanne Miller/Steven Robbins
Product Manager/PM Team Reviewer (23)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/13/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 8/13/92
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

for Marcia van Gemert, Ph.D. James W. Rowe 8/13/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Du Pont
Chemical: Methyl-3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-2-thiophene carboxylate and Methyl-2-[[[[N(4-methoxy-6-methyl-1,3,5-triazin-2-yl)methylamino]carbonyl]amino]sulfonyl]benzoate

Synonym: thifensulfuron methyl (formerly DPX-M6316); tribenuron methyl (formerly DPX-L5300)
Submission: S411238/S411242
DP Barcode: D174241/D174245
Caswell No.: 573S/419S/419H
Identifying No.: 1F03961/1F03962
Shanghnessy No.: 128845/128887/122010
MRID No.: 421577-00 and 421577-01
Action Requested: Please review this submission which is in response to the review done by Linda Taylor on September 24/20, 1991. Please review this data and advise as to its acceptability. Please note this data is also for support of 1F03961/1F03962.

Background: Harmony® Extra Herbicide is registered for use on wheat

and barley. Both Thifensulfuron and Tribenuron have established permanent tolerances on barley and wheat grain and straw, and Thifensulfuron is registered for use on soybeans. The toxicology data available to support this request are listed in Table A.
In the previous TB II review (cited above) of the two petitions proposing tolerances for Thifensulfuron methyl and Tribenuron methyl residues in or on oat grain and straw resulting from the use of DuPont Harmony® Extra Herbicide to control certain weeds in oats, several data gaps were specified [eye and dermal irritation for both Thifensulfuron and Metsulfuron methyl and dermal sensitization and mutagenicity (Category III) for Metsulfuron methyl]. The latter compound (Shaughnessy No. 122010; CASWELL # 419H) is a plant metabolite of tribenuron. In the current submission, the Registrant provided MRID #'s for two dermal irritation studies (Metsulfuron methyl and thifensulfuron methyl), two eye irritation studies (Metsulfuron methyl and thifensulfuron methyl), a dermal sensitization study (Metsulfuron methyl), and a mutagenicity study (Metsulfuron methyl). With the exception of the latter study (discussed in the previous TB II review of these petitions), these studies had never been submitted to TB II for review. These were obtained for this current action and have been reviewed. The DER's are appended.

With regard to Metsulfuron methyl, the issue raised by this reviewer in the previous review was not whether it should be included in the tolerance, but whether there is a need to amend the registration for Metsulfuron methyl itself to include oat grain and straw in the list of commodities where it is allowed to occur. This reviewer questioned whether an oat product would be in violation if Metsulfuron methyl were detected. This issue will be addressed by Chemistry Branch I - Tolerance Support. NOTE: Although Metsulfuron methyl is not the subject per se of the current submission, MRID numbers for two studies on Metsulfuron methyl, which had not been submitted to TB II previously for review, were included in the current submission. TB II has review these studies, along with those on Thifensulfuron methyl, and they are included in the current TB II response.

With regard to the Registrant's discussion of the dietary risk and whether the RfD's would be exceeded by the proposed use, this is the purview of the Dietary Exposure Section of the Science Analysis Branch of HED and, to date, TB II has not received a copy of their assessment of the petitions.

The studies cited by the petitioner that had not been reviewed by TB II previously are summarized below.

MRID # 409215-01 (Primary eye irritation study in rabbits with thifensulfuron methyl): The test material caused mild conjunctival redness and slight chemosis in all six rabbits and slight corneal opacity and moderate iritis in one of the 6 rabbits. Biomicroscopic examinations revealed no corneal injury throughout the study. All

ocular irritation had resolved by 24 hours after treatment. The mean eye irritation score was 9.8 (range of 4-39). (TOXICITY CATEGORY - IV); This study is classified Core supplementary, pending submission of the Batch # of the test material utilized in the study, individual body weight/clinical signs data, and information on the physical properties of the test material; i.e., whether the test material was ground into a fine powder before testing. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it may be upgraded .

MRID # 409215-02 (Primary dermal irritation study in rabbits with thifensulfuron methyl): Under the conditions of the study, test material (thifensulfuron methyl) was a slight dermal irritant. (TOXICITY CATEGORY - IV); This study is classified Core supplementary, pending submission of the Batch # of the test material utilized in this study and individual body weight/ clinical signs data. This study does not satisfy the guideline requirement (81-5) for a primary dermal irritation study in rabbits, but it may be upgraded.

MRID # 408588-01 (Primary eye irritation study with metsulfuron methyl): The test material (metsulfuron methyl) produced corneal opacity in one rabbit, mild conjunctival redness in all 6 rabbits, and slight chemosis in one rabbit. Biomicroscopic examinations were negative for corneal injury throughout the study. All treated eyes were normal by 72 hours after treatment. (TOXICITY CATEGORY - III). This study is classified Core supplementary, pending submission of the Batch # of the test material utilized in this study, individual body weight/clinical signs data, and information on the physical properties of the test material; i.e., whether the test material was ground into a fine powder before testing. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it may be upgraded.

MRID # 408588-02 (Primary dermal irritation study with metsulfuron methyl): Under the conditions of the study, test material (metsulfuron methyl) did not produce any dermal irritation. (TOXICITY CATEGORY - IV). This study is classified Core supplementary, pending submission of the Batch # of the test material utilized in this study and individual body weight/ clinical signs data. This study does not satisfy the guideline requirement (81-5) for a primary dermal irritation study in rabbits, but it may be upgraded.

MRID # 408588-03 (Dermal sensitization study in guinea pigs with metsulfuron methyl): Under the conditions of the study, the test material did not produce delayed hypersensitivity or allergic reactions in guinea pigs. Slight patchy erythema was observed in 2 treated (♂♂) animals 24 hours after the first of three induction treatments; no other dermal irritation was displayed during the induction phase. No dermal irritation was observed in the vehicle

control throughout the study. The positive control displayed a strong dermal irritation reaction, especially after the second and third induction treatments. During the challenge phase, one test material guinea pig (9) displayed slight patchy erythema by 48 hours after treatment. The negative and positive controls displayed their respective expected results. This study is classified Core supplementary, pending submission of the Batch # of the test material used in this study. This study does not satisfy the guideline requirement (81-6) for a dermal sensitization study, but it may be upgraded.

Data Gaps: By current standards, the data gaps remain the same as before, although the new studies are all upgradeable. No additional data/information have been submitted to TB II for review regarding the mutagenicity (Category III) study on Metsulfuron methyl.

Tolerance Summary: A Data Residue Evaluation System (DRES) analysis will be performed for the current request for residues of Thifensulfuron methyl in oat grain and straw. Additionally, a similar analysis will be run for Tribenuron methyl.

Acceptable Daily Intake: The Reference Dose (RfD) for Thifensulfuron methyl is 0.013 mg/kg body weight/day, based on the NOEL of 1.25 mg/kg/day from a 2-year rat feeding study and a 100-fold safety factor. The Reference Dose (RfD) for Tribenuron methyl is 0.0063 mg/kg body weight/day, based on the NOEL of 0.625 mg/kg/day from a 1-year dog study and a 100-fold safety factor. The total amount of tolerance should not exceed 100% of the RfD of either a.i..

Effect of Tolerance on ADI: DRES will calculate the effect of this tolerance request on both RfD's.

Regulatory Actions Pending: TB II is not aware of any.

CONCLUSION

TB II has no objection to the request for registration of the new use of Du Pont Harmony® Extra Herbicide on oats and a tolerance for Thifensulfuron methyl and Tribenuron methyl on oat grain and straw, provided neither RfD is exceeded as a result of these residue levels and the outstanding data requirements (primary eye and dermal irritation and dermal sensitization studies) are fulfilled with respect to thifensulfuron methyl.

TABLE A

DATA AVAILABLE

Thifensulfuron methyl	
A. Acute oral LD_{50} - rat	LD_{50}>5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}>2000 mg/kg Tox.Cat.IV
C. Acute inhalation LC_{50} - rat	LC_{50}=7.9 mg/L/4 hr Tox.Cat.3
D. Primary eye irritation - rabbit	supplementary, pending submission of Batch # of test material, individual body weights/clinical signs data, & information of whether test material was ground into a fine powder prior to testing
E. Primary dermal irritation - rabbit	supplementary, pending submission of Batch # of test material, individual body weight/clinical signs data
F. Dermal sensitization - guinea pig	no study located
G. 90-day feeding - rat	systemic NOEL=100 ppm, LEL=2500 ppm, based on ↓ body weight, clinical pathology
H. 13-week subchronic - dog	NOEL=1500 ppm,LEL=7500 ppm, based on ↓ body & adrenal weights in males
I. Developmental toxicity - rat	maternal NOEL=725 mg/kg HDT fetotoxic NOEL=159 mg/kg, LEL=725 mg/kg, based on ↑ incidence of small renal papillae; teratogenic NOEL=159 mg/kg, LEL=725 mg/kg, based on absence of renal papillae
J. Developmental toxicity - rabbit	maternal NOEL=158 mg/kg, LEL=511 mg/kg, based on ↓ body-weight gain; developmental NOEL=511 mg/kg HDT
K. Chronic toxicity - dog	NOEL=750 ppm, LEL=7500 ppm, based on ↓ body weight/body-weight gain in males & ↑ liver weight
L. 2-Generation reproduction - rat	systemic NOEL=2500 ppm HDT reproductive NOEL=2500 ppm
M. Chronic tox/carcinogenicity - rat	systemic NOEL=25 ppm, LEL=500 ppm, based on ↓ Na levels, body weight/BW gains; negative for carcinogenicity

N. Carcinogenicity - mouse		systemic NOEL=25 ppm, LEL=750 ppm, based on ↓ body-weight gains; negative for carcinogenicity
O. Mutagenicity -	Category I	not mutagenic with/without metabolic activation
	Category II	negative for clastogenic response at 5000 mg/kg
	Category III	did not induce significant ↑ in UDS in primary rat hepatocytes
P. Metabolism		excretion mainly as parent, mostly in urine/feces; no apparent tissue accumulation, although the majority is not eliminated until 48 hours post dose; metabolites: triazine amine, O-demethyl DPX-M6316, thiophene sulfonamide, DPX-M6316 acid, 2-acid-3-sulfonamide

Tribenuron methyl

A. Acute oral LD_{50} - rat	LD_{50}> 5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}> 2000 mg/kg Tox.Cat.IV
C. Acute inhalation LD_{50} - rat	LC_{50}> 6.7 mg/L/4hr Tox.Cat.3
D. Primary eye irritation - rabbit	opacity/irrit. clear within 72 hrs Tox.Cat.III
E. Primary dermal irritation - rabbit	irrit. cleared by 72 hours Tox.Cat. III
F. Dermal sensitization - guinea pig	nonsensitizing
G. 90-day feeding - rat	systemic NOEL=100 ppm, LEL=1750 ppm, based on ↓ BWG & FC/FE, heart/brain/ liver/ kidney wts.; ↑ rel. organ wts.; ↓ glucose & cholesterol
H. 13-week subchronic - dog	NOEL>2500 ppm HDT (62.5 mg/kg)
I. Developmental toxicity - rat	maternal NOEL=20 mg/kg, LEL=125 mg/kg, based on ↓ BWG and FC, ↑ rel. liver wt. develop. NOEL= 20 mg/kg, LEL= 125 mg/kg, based on ↓ body weight; at highest dose, ↑ resorptions & fetal death, incomplete ossification; doses tested:20/125/500 mg/kg
J. Developmental toxicity - rabbit	maternal NOEL= 20 mg/kg, LEL= 80 mg/kg HDT, ↓ FC,

	↑ abortions; develop. NOEL=20 mg/kg, LEL=80 mg/kg HDT, 10% ↓ BW; no terata; doses 5, 20, 80 mg/kg
K. Chronic toxicity - dog	NOEL= 25 ppm (0.625 mg/kg), LEL= 250 ppm, based on ♂/♀ ↑ bilirubin & AST levels, ♂ ↑ urinary vol., ♀ ↑ globulin & ↓ BWG
L. 2-Generation reproduction - rat	paternal NOEL= 25 (1.25 mg/kg), LEL=250 ppm, based on ↓ BWG in F1 ♀; reproductive NOEL= 25 ppm, LEL=250 ppm, based on ↓BWG during lact. for F1b & F2b pups; developmental NOEL = 25 ppm, LEL=250 ppm, based on ↓ spleen wt in F2b pups
M. Chronic tox/carcinogenicity - rat	systemic NOEL= 25 ppm (1.25 mg/kg), LEL=250 ppm, based on ↓ BWG ♂/♀; + for carcinogenicity; ↑ mammary gland adenocarcinomas in ♀; dosed: 25, 250, 1250 ppm SAP Category D carcinogen HED Peer Review Category C
N. Carcinogenicity - mouse	systemic NOEL= 200 ppm (3 mg/kg), LEL=1500 ppm, based on ↑ incidence of seminiferous degeneration & oligospermia, 10% ↓ BWG at 90 days; negative for carcinogenicity
O. Mutagenicity - Category I	not mutagenic
Category II	not mutagenic
Category III	not mutagenic
P. Metabolism	readily absorbed; major route of excretion-urine; no apparent accumulation; major metabolites: metsulfuron, saccharin, 0-demethyl triazine amine

Harmony® Extra Herbicide

A. Acute oral LD_{50} - rat	LD_{50}>5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}> 2000 mg/kg Tox.Cat.III
C. Acute inhalation LD_{50} - rat	no study submitted*
D. Primary eye irritation - rabbit	moderately irrit.Tox.Cat.III
E. Primary dermal irritation - rabbit	PII 0.5; Tox.Cat. IV
F. Dermal sensitization - guinea pig	nonsensitizing

*less than 0.5% of granules are < 105 micron diameter

Metsulfuron methyl

A. Acute oral LD_{50} - rat	LD_{50}> 5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}> 2000 mg/kg Tox.Cat.III
C. Acute inhalation LD_{50} - rat	LC_{50}> 5.3 mg/L/4 hr Tox.Cat.
D. Primary eye irritation - rabbit	supplementary, pending submission of Batch # of test material, individual body weight/clinical signs data, & information of whether test material was ground into a fine powder before testing
E. Primary dermal irritation - rabbit	supplementary, pending submission of Batch # of test material, individual body weight/clinical signs data
F. Dermal sensitization - guinea pig	supplementary, pending submission of Batch # of test material used
G. 21-Day dermal - rabbit	dermal irritation at 500/2000 mg/kg (6 hr/day) & at 2000 mg/kg after 14-day recovery period; dermal irritation NOEL=125 mg/kg, LEL=500 mg/kg; systemic NOEL=500 mg/kg, LEL=2000 mg/kg, based on diarrhea
H. 90-day feeding - rat	study classified supplementary, but chronic study is acceptable
I. 13-week subchronic - dog	there is a 1-year study
J. Developmental toxicity - rat	maternal NOEL< 40 mg/kg, hyperactivity/ungroomed coat; fetotoxic NOEL>1000 mg/kg; developmental NOEL> 1000 mg/kg
K. Developmental toxicity - rabbit	maternal NOEL= 25 mg/kg, LEL= 100 mg/kg, based on decreased body weight & death; fetotoxic NOEL > 700 mg/kg; developmental NOEL > 700 mg/kg HDT
L. Chronic toxicity - dog	NOEL= 50 ppm, LEL= 500 ppm, based on decreased serum LDH
M. 2-Generation reproduction - rat	systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body-weight gain; reproduct. NOEL > 5000 ppm HDT
N. Chronic tox/carcinogenicity - rat	systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body weight; no increase in

O. Carcinogenicity - mouse		tumors systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body weight; no increase in tumors
P. Mutagenicity -	Category I	Ames assay - negative
	Category II	chrom. aber. CHO/rat bone marrow aber./mouse micronucleus - negative
	Category III	no acceptable study
Q. Metabolism - rat		rapid elimination, mostly in urine, largely unchanged

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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/13/92
Review Section II, Toxicology Branch II/HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 8/13/92
Section II Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation-rabbits (81-5)

CASWELL NUMBER: 573S SHAUGHNESSY NO.: 128845

MRID NUMBER: 409215-02

TEST MATERIAL: 2-thiophenecarboxylic acid, 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-,methyl ester

SYNONYMS: IN M6316-25; DPX-M6316; Thifensulfuron methyl

STUDY NUMBER: HLR 649-87; Medical Research # 4581-562

SPONSOR: DuPont Agricultural Products Department

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: Primary Dermal Irritation Study with IN M6316-25 in Rabbits

AUTHOR(S): WJ Brock

REPORT ISSUED: December 10, 1987

QUALITY ASSURANCE: A quality assurance statement and a statement of compliance with FIFRA Good Laboratory Practice Standards were signed and dated.

CONCLUSION: Under the conditions of the study, test material was a slight dermal irritant.

TOXICITY CATEGORY - IV

CLASSIFICATION: Core supplementary, pending submission of the Batch # of the test material utilized in this study and individual body weight/ clinical signs data. This study does not satisfy the guideline requirement (81-5) for a primary dermal irritation study in rabbits, but it may be upgraded.

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I. MATERIALS

1. Test compound: 2-thiophenecarboxylic acid, 3-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]aminosulfonyl]-methyl ester; Description: off-white solid; Batch #: not provided, Haskell # 16,972, CAS Registry #: 79277-27-3; Purity: 95.6%.

2. Test animals: Species: rabbits; Strain: New Zealand white; Age: young adult; Weight: 2625-3130 grams; Source: Hare Marland, Hewitt, NJ.

II. METHODS

Six male rabbits (quarantined for ≈ 2 weeks prior to study; Purina Certified Rabbit Chow® # 5322 and water available ad libitum, except during exposure) were utilized for the study. One day prior to the study, the hair of these rabbits was clipped closely to expose the skin from the scapular to the lumbar region of the back. Each rabbit was placed into a stock (where it remained throughout the exposure period), which was fitted with a piece of rubber sheeting (≈ 8" x 18"). A 0.5 gram aliquot of IN M6316-25 was applied directly to each test site beneath a 1-inch gauze square that was held in place with tape. The rubber sheeting was then wrapped around the rabbit and secured with clips to retard evaporation and to keep the test material in contact with the skin without undue pressure. Three other test materials were applied to 3 other sites on the same animal.

Approximately 4 hours after application, the rubber sheeting was loosened, the test site was marked with a waterproof pen (apparently in order to identify each test material), and the wrappings and gauze squares were removed. The test sites were washed gently with warm water to remove excess test material, gently wiped dry, evaluated after ≈ 4, 24, 48, and 72 hours for erythema, edema, and other evidence of dermal effects, and were scored according to the Draize scale. Adjacent areas of untreated skin were used for comparison. The skin was shaved as needed to facilitate evaluation of irritation during the 72-hour observation period. Primary irritation indices were calculated for each rabbit, based on the method presented in the Federal Hazardous Substances Act Regulations (16 CFR 1500).

III. RESULTS

The test material produced slight erythema in 5 rabbits by 4 hours post dose; by 24 hours, all rabbits exhibited slight erythema with 2 rabbits exhibiting slight edema as well. No dermal irritation was displayed by any of the rabbits by 48 hours. The Primary Dermal Irritation Scores for the rabbits ranged from 0.5 to 1.0

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Summary of Skin Responses

Response/grade/ hours post dose	Erythema				Edema			
	4	24	48	72	4	24	48	72
slight	5/6	6/6	0/6	0/6	0/6	2/6	0/6	0/6
no response	1/6	0/6	6/6	6/6	6/6	4/6	6/6	6/6

IV. CONCLUSIONS

The test material was a slight dermal irritant. The mean score [Primary Irritation Index] was 0.67 (slight).

Toxicity Category - IV.

V. CLASSIFICATION:

Core Supplementary. This study does not satisfy the guideline requirements (§81-5) for a primary dermal irritation study in rabbits, but it may be upgraded with the submission of the Batch # of the test material used in this study and individual body weight/clinical signs data.

VI. STUDY DEFICIENCIES

The Batch # of the test material was not provided, nor were body weight/clinical signs data. Additionally, the skin was not evaluated at one hour post dose.

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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/10/92
Review Section II, Toxicology Branch II/HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 8/13/92
Section II Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation-rabbits (81-4)

CASWELL NUMBER: 573S

MRID NUMBER: 403215-01

TEST MATERIAL: 2-thiophenecarboxylic acid, 3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-methyl ester

SYNONYMS: IN M6316-25; DPX-M6316; thifensulfuron methyl

STUDY NUMBER: HLR 529-87; Medical Research # 4581-562

SPONSOR: DuPont Agricultural Products Department

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: Primary Eye Irritation Study with IN M6316-25 in Rabbits

AUTHOR(S): WJ Brock

REPORT ISSUED: November 16, 1987

CONCLUSION: The test material caused mild conjunctival redness and slight chemosis in all six rabbits and slight corneal opacity and moderate iritis in one of the 6 rabbits. Biomicroscopic examinations revealed no corneal injury throughout the study. All ocular irritation had resolved by 24 hours after treatment. The mean eye irritation score was 9.8 (range of 4-39).

TOXICITY CATEGORY - IV

CLASSIFICATION: Core supplementary, pending submission of the Batch # of the test material utilized in the study, individual body weight/clinical signs data, and information on the physical properties of the test material; i.e., whether the test material was ground into a fine powder before testing. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it may be upgraded .

I. MATERIALS

1. Test compound: 2-thiophenecarboxylic acid, 3-[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-methyl ester; Description: off-white solid; Batch #: not provided, Haskell # 16,972, CAS Registry #: 79277-27-3; Purity: 95.6%.

2. Test animals: Species: rabbits; Strain: New Zealand white; Age: young adult; Weight: 2591-2964 grams; Source: Hare Marland, Hewitt, NJ.

II. METHODS

Six male rabbits (quarantined for ≈2 weeks prior to study; Purina Certified Rabbit Chow® # 5322 and water available ad libitum) were utilized for the study. One day prior to the study, the eyes of these rabbits were examined using fluorescein dye to determine whether any had a preexisting corneal or conjunctival injury or irritation. An ≈ 35 mg aliquot (a weight corresponding to a 0.1 mL volume of test material) of IN M6316-25 was introduced into the lower conjunctival sac of the left eye of each rabbit. The right eye served as the control. Neither the treated nor the control eye was washed. The rabbits were examined for evidence of eye irritation ≈ 1, 24, 48, and 72 hours after treatment. Observations of each eye at each time point were made using illumination and magnification and scored for ocular reactions using the Draize scale. Biomicroscopic examinations for corneal injury were conducted at the 24-hour observation and each subsequent observation period. Treated eyes were scored according to the system presented in Table II, copy appended.

III. RESULTS

The test material produced slight corneal opacity and moderate iritis in one rabbit and mild conjunctival redness and slight chemosis in all 6 rabbits. Biomicroscopic examinations were negative for corneal injury throughout the study. All treated eyes were normal by 24 hours after treatment. The results are listed in the table below.

Eye irritation reactions after IN M6316-25 exposure

Treatment	Cornea	Iris	Conjunctiva
Unwashed eye	Slight (generalized) opacity in 1 rabbit at 1 hour only (this rabbit also displayed reactions in the iris and conjunctiva)	one rabbit showed moderate involvement	redness: observed in all rabbits at 1 hour; chemosis: observed in all rabbits at 1 hour.

A quality assurance statement and a statement of compliance with FIFRA Good Laboratory Practice Standards were signed and dated.

IV. CONCLUSIONS

The test material caused mild conjunctival redness and slight chemosis in all six rabbits and slight corneal opacity and moderate iritis in one of the 6 rabbits. Biomicroscopic examinations revealed no corneal injury throughout the study. All ocular irritation had resolved by 24 hours after treatment. The mean eye irritation score was 9.8 (range of 4-39).

Toxicity Category - IV.

V. CLASSIFICATION:

This study does not satisfy the guideline requirements (§81-4) for a primary eye irritation study in rabbits, but it may be upgraded with the submission of the Batch # of the test material utilized in the study, individual body weight/clinical signs data, and information on whether the test material was ground into a fine powder before testing.

VI. STUDY DEFICIENCIES

There was no information on whether the test material, which was stated to be an off-white solid, was ground into a fine dust before being introduced into the eyes. Additionally, individual body weight /clinical signs data and the Batch # of the test material were not provided.

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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 7/29/92
Review Section II, Toxicology Branch II/HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 8/5/92
Section II Head, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal sensitization - guinea pigs

CASWELL NUMBER: 419H

MRID NUMBER: 408588-03

TEST MATERIAL: benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-, methyl ester

SYNONYMS: IN T6376-41; metsulfuron methyl; DPX-T6376

STUDY NUMBER: HLR 711-87; Medical Research # 4581-651

SPONSOR: DuPont Agricultural Products Department

TESTING FACILITY: Haskell Laboratory for Toxicology & Industrial Medicine

TITLE OF REPORT: Closed-Patch Repeated Insult Dermal Sensitization Study (Buehler Method) with IN T6376-42 in Guinea Pigs

AUTHOR(S): William J. Brock

REPORT ISSUED: December 18 1987

Quality Assurance: A quality assurance statement was provided.

CONCLUSION: Under the conditions of the study, the test material did not produce delayed hypersensitivity or allergic reactions in guinea pigs. Slight patchy erythema was observed in 2 treated (♂♂) animals 24 hours after the first of three induction treatments; no other dermal irritation was displayed during the induction phase. No dermal irritation was observed in the vehicle control throughout the study. The positive control displayed a strong dermal irritation reaction, especially after the second and third induction treatments. During the challenge phase, one test material guinea pig (♀) displayed slight patchy erythema by 48 hours after treatment. The negative and positive controls displayed their respective expected results.

CLASSIFICATION: Core-Supplementary. This study does not satisfy the guideline requirement (81-6) for a dermal sensitization study, but it may be upgraded following the submission of the Batch # of the test material used in this study.

I. MATERIALS

1. Test compound: benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-, methyl ester; Description: white solid; Batch #: not indicated, Haskell #: 16,967; Purity: 95.8%.

2. Test animals: Species: Albino guinea pigs; Strain: Duncan Hartley; Age: young adult; Weight: range-finding study (456-474 grams), main study, induction phase [test material group (350-456 grams), vehicle control (374-446 grams), positive control (461-541 grams)], challenge phase [negative control (365-460 grams)]; Source: Charles River Breeding Laboratories, Stone Ridge, NY.

II. METHODS

A. General: Prior to initiation of the study, a range-finding study was performed on 2 male/2 female guinea pigs to determine the primary irritation potential of the test material. It was found that the test material was not an irritant at any of the test sites (0.4 mL of the neat material and 25, 10, and 5% (w/v) suspensions in dimethyl phthalate) ≈ 24 hours after treatment. Therefore, the neat test material was used for the main study. The test animals were provided with Purina Certified Guinea Pig Chow® # 5026 and water ad libitum. There was no information provided as to how the animals were chosen for the various groups. Body weights were recorded weekly. The main study consisted of two phases: an induction and a challenge phase.

A. Induction Phase: In the induction phase, 0.4 mL of the neat test material (slightly moistened with dimethyl phthalate) was applied onto the shaved, intact skin of the back (test site size not provided) of each of twenty guinea pigs (10/sex) under a 25 mm Hill Top Chamber Delivery System® (patch). A piece of plastic wrap was placed over the patch, and each animal was then wrapped with adhesive bandage. After ≈ a 6-hour exposure period, the bandages and patches were removed from each animal and the test sites were washed gently with warm water to remove excess test material. Irritation responses were scored ≈ 24 and 48 hours after treatment. This induction procedure was performed once a week for 3 consecutive weeks (total of three 6-hour treatments with the neat test material). The vehicle control [5/sex, 0.4 mL of dimethyl phthalate] and the positive control [3 ♂♂/2 ♀♀, 0.4 mL of a suspension of DNCB [benzene, 1-chloro-2,4-dinitro-; 0.3% in 80% ethanol in water] groups were subjected to the same procedures.

C. Challenge Phase: Two weeks after the final induction treatment, the test animals were challenged for sensitization by applying 0.4 mL of the neat test material, slightly moistened with dimethyl phthalate, onto an unexposed test site on the shaved, intact skin of each back under a patch, a piece of plastic wrap placed over the patch, with subsequent wrapping of the animal as before. The vehicle and positive control animals were handled similarly by applying 0.4 mL of dimethyl phthalate and 0.4 mL of a 0.3%

suspension of DNCB in 80% ethanol (in water), respectively. Concurrently, 10 guinea pigs (5/sex) were treated with 0.4 mL of the neat test material moistened with dimethyl phthalate and served as negative controls. After ≈ a 6-hour exposure period, the bandages were removed, and the test sites were washed as before. Approximately 22 hours after treatment, the test sites were depilated with a depilatory, which was applied to the test site and surrounding area where it remained for ≈ 30 minutes, after which the sites were gently washed as before and gently patted dry. Irritation responses were scored ≈ 2 hours after this latter procedure and again 48 hours after treatment.

D. Evaluation Procedures: With regard to how the test sites were evaluated, the incidence of sensitization was defined as the number of animals in each group sensitized to the test material divided by the total number of animals tested in that group. Severity of the irritation response was reported as the sum of the test scores in each group divided by the total number of animals tested in that group for both the 24- and 48-hour evaluations. The scoring of the responses was according to the system shown below.

SKIN REACTION	SCORE
no reaction	0
slight patchy erythema	1
slight/confluent or moderate/patchy erythema	2
moderate erythema	3
severe erythema with or without edema	4

III. RESULTS

Guinea pigs in all groups gained weight during the study, but the positive controls displayed the smallest gains. During the induction phase of the study, two test material guinea pigs displayed slight patchy erythema 24 hours after the first induction treatment. There was no other dermal irritation displayed in this group or in any of the vehicle control animals during the induction phase. The positive control exhibited slight patchy erythema to severe erythema, necrosis, and edema during the induction phase. In the challenge phase of the study, no dermal irritation was observed in the vehicle or negative control animals. One test material guinea pig displayed slight patchy erythema by 48 hours after treatment (not one of the two who displayed dermal irritation during the induction phase). No other dermal irritation was observed in the test material group and none was displayed in either the vehicle or negative control animals during the challenge phase. No sensitization response was observed in the test material animals; the severity of the irritation response was 0.1 at 48 hours following challenge. The positive control animals displayed moderate to severe erythema, necrosis, blanching, and edema during the challenge phase. The incidence of sensitization in the positive control was 1.0, and the severity of the response ranged from 3.6 to 3.8.

NOTE: It appears that the concentration of the positive control chosen for use in the induction phase was too high, in light of the responses observed after the second and third inductions.

Skin Responses♦

Group/Phase	IN T6376-41			Positive control♥		
	#1	#2	#3	#1	#2	#3
Induction Phase						
24 hours	1/2♂	0	0	1/4,2/1,ED/5	2/2,3/2,4/1,ED/5,N/5	3/2,4/3,ED/5,N/3
48 hours	0	0	0	1/2/,2/3,D/5	2/2,3/1,4/2,ED/5,N/5	3/1,4/4,ED/5,N/3
Challenge Phase						
24 hours	0			3/1,4/4,ED/4,N/1,B/4		
48 hours	1/1♀			3/2,4/3,ED/4,N/3,B/1		

♦ no reaction=0; slight patchy erythema=1; slight/confluent or moderate/patchy erythema=2; moderate erythema=3; severe erythema with or without edema=4; ED=edema; B=blanching; N=necrosis; ♥ response/# showing response

IV. CONCLUSIONS

Under the conditions of the study, the test material did not produce delayed hypersensitivity or allergic reactions in guinea pigs following exposure (3 induction treatments with the neat test material followed by a challenge with the neat test material). Slight patchy erythema was observed in 2 treated (♂♂) animals 24 hours after the first induction treatment; no other dermal irritation was displayed during the induction phase. No dermal irritation was observed in the vehicle control throughout the study. The positive control displayed a strong dermal irritation reaction, especially after the second and third induction treatments. During the challenge phase, one test material guinea pig (♀) displayed slight patchy erythema by 48 hours after treatment. The negative and positive controls displayed their respective expected results.

V. CLASSIFICATION

Core-Supplementary. This study does not satisfy the guideline requirement (81-6) for a dermal sensitization study, but it may be upgraded following the submission of the Batch # of the test material used in this study.

009687

Reviewed by: Linda L. Taylor, Ph.D 7/29/92
Review Section II, Toxicology Branch II/HED (H7509C)
Secondary Reviewer: K. Clark Swentzel 8/4/92
Section II Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation-rabbits (81-5)

CASWELL NUMBER: 419H

MRID NUMBER: 408588-02

TEST MATERIAL: benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-,methyl ester

SYNONYMS: IN T6376-41; metsulfuron methyl; DPX-T6376

STUDY NUMBER: HLR 646-87; Medical Research # 4581-561

SPONSOR: DuPont Agricultural Products Department

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: Primary Dermal Irritation Study with IN T6376-41 in Rabbits

AUTHOR(S): WJ Brock

REPORT ISSUED: November 16, 1987

QUALITY ASSURANCE:A quality assurance statement and a statement of compliance with FIFRA Good Laboratory Practice Standards were signed and dated.

CONCLUSION: Under the conditions of the study, test material did not produce any dermal irritation.

TOXICITY CATEGORY - IV

CLASSIFICATION: Core supplementary, pending submission of the Batch # of the test material utilized in this study and individual body weight/ clinical signs data. This study does not satisfy the guideline requirement (81-5) for a primary dermal irritation study in rabbits, but it may be upgraded.

009687

I. MATERIALS

1. Test compound: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]aminosulfonyl]-methyl ester; Description: white solid; Batch #: not provided, Haskell # 16,967, CAS Registry #: 74223-64-6; Purity: 95.8%.

2. Test animals: Species: rabbits; Strain: New Zealand white; Age: young adult; Weight: 2965-3403 grams; Source: Hazleton Research Products, Inc., Denver, PA.

II. METHODS

Six male rabbits (quarantined for ≈ 2 weeks prior to study; Purina Certified Rabbit Chow® # 5322 and water available ad libitum, except during exposure) were utilized for the study. One day prior to the study, the hair of these rabbits was clipped closely to expose the skin from the scapular to the lumbar region of the back. Each rabbit was placed into a stock (where it remained throughout the exposure period), which was fitted with a piece of rubber sheeting (≈ 8" x 18"). A 0.5 gram aliquot of IN T6376-41 moistened with dimethyl phthalate was applied directly to a 1-inch gauze square, which was placed on the test site of each rabbit and held in place with tape. The rubber sheeting was then wrapped around the rabbit and secured with clips to retard evaporation and to keep the test material in contact with the skin without undue pressure. NOTE: On page 7 of the report it states: "Three other test material wre(sic) applied to 3 other sites on the same animal." This is assumed to mean that three additional test materials were applied and not 3 other samples of IN T6376-41.

Approximately 4 hours after application, the rubber sheeting was loosened, the test site was marked with a waterproof pen, and the wrappings and gauze squares were removed. The test sites were washed gently with warm water to remove excess test material, gently wiped dry, evaluated after ≈ 4, 24, 48, and 72 hours for erythema, edema, and other evidence of dermal effects, and were scored according to the Draize scale. Adjacent areas of untreated skin were used for comparison. The skin was shaved as needed to facilitate evaluation of irritation during the 72-hour observation period. Primary irritation indices were calculated for each rabbit, based on the method presented in the Federal Hazardous Substances Act Regulations (16 CFR 1500).

III. RESULTS

The test material did not produce any dermal irritation in any of the rabbits at any time period.

IV. CONCLUSIONS

The test material did not cause any dermal irritation in any of the six rabbits. The mean score [Primary Irritation Index] was 0 (Negligible).

Toxicity Category - IV.

009687

V. CLASSIFICATION:

This study does <u>not</u> satisfy the guideline requirements (§81-5) for a primary dermal irritation study in rabbits, but it may be upgraded with the submission of the Batch # of the test material used in this study and individual body weight/clinical signs data.

VI. STUDY DEFICIENCIES

The Batch # of the test material was not provided, nor were body weight/clinical signs data. Additionally, the skin was not evaluated at one hour post dose.

009687

Reviewed by: Linda L. Taylor, Ph.D Linda Lee Taylor 7/29/92
Review Section II, Toxicology Branch II/HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K Clark Swentzel 8/5/92
Section II Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation-rabbits (81-4)

CASWELL NUMBER: 419H

MRID NUMBER: 408588-01

TEST MATERIAL: benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-,methyl ester

SYNONYMS: IN T6376-41; metsulfuron methyl; DPX-T6376

STUDY NUMBER: HLR 630-87; Medical Research # 4581-561

SPONSOR: DuPont Agricultural Products Department

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: Primary Eye Irritation Study with IN T6376-41 in Rabbits

AUTHOR(S): WJ Brock

REPORT ISSUED: November 16, 1987

CONCLUSION: The test material produced corneal opacity in one rabbit, mild conjunctival redness in all 6 rabbits, and slight chemosis in one rabbit. Biomicroscopic examinations were negative for corneal injury throughout the study. All treated eyes were normal by 72 hours after treatment.

TOXICITY CATEGORY - III

CLASSIFICATION: Core supplementary, pending submission of the Batch # of the test material utilized in this study, individual body weight/clinical signs data, and information on the physical properties of the test material; i.e., whether the test material was ground into a fine powder before testing. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it may be upgraded.

I. MATERIALS

1. Test compound: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]aminosulfonyl]-methyl ester; Description: white solid; Batch #: not provided, Haskell # 16,967, CAS Registry #: 74223-64-6; Purity: 95.8%.

2. Test animals: Species: rabbits; Strain: New Zealand white; Age: young adult; Weight: 2728-2838 grams; Source: Hare Marland, Hewitt, NJ.

II. METHODS

Six female rabbits (quarantined for ≈2 weeks prior to study; Purina Certified Rabbit Chow® # 5322 and water available ad libitum) were utilized for the study. One day prior to the study, the eyes of these rabbits were examined using fluorescein dye to determine whether any had a preexisting corneal or conjunctival injury or irritation. A 50 mg aliquot of IN T6376-41 was introduced into the lower conjunctival sac of the left eye of each rabbit. NOTE: It was stated that the weight equivalent of 0.1 mL, an EPA criterion for testing the eye irritation potential of a compound, was 35 mg, but since that was less than what is typically used, a 50 mg aliquot was selected for testing. The right eye served as the control. Neither the treated nor the control eye was washed. The rabbits were examined for evidence of eye irritation ≈ 1, 24, 48, and 72 hours after treatment. Observations of each eye at each time point were made using illumination and magnification and scored for ocular reactions using the Draize scale. Biomicroscopic examinations for corneal injury were conducted at the 24-hour observation and each subsequent observation period. Treated eyes were scored according to the system presented in Table II, copy appended.

III. RESULTS

The test material produced slight corneal opacity in one rabbit, slight chemosis in another rabbit, and mild conjunctival redness in all 6 rabbits. Biomicroscopic examinations were negative for corneal injury throughout the study. All treated eyes were normal by 72 hours after treatment. The results are listed in the table below.

Eye irritation reactions after IN T6376-41 exposure

Treatment	Cornea	Iris	Conjunctiva
Unwashed eye	Slight (localized) opacity in 1 rabbit at 1 hour only (this rabbit displayed redness of conjunctiva at 1, 24, & 48 hours)	no involvement	redness: observed in all rabbits at 1 hour, in 3 only at 1 hour, in 2 at 1 & 24 hours, in 1 at 1, 24, & 40 hours; chemosis: observed in 1 rabbit at 1 hour only (this rabbit displayed redness at 1 and 24 hours)

A quality assurance statement and a statement of compliance with FIFRA Good Laboratory Practice Standards were signed and dated.

IV. CONCLUSIONS

The test material caused slight corneal opacity in one rabbit, slight chemosis in another rabbit, and mild conjunctival redness in all six rabbits. Biomicroscopic examinations revealed no corneal injury at any of the observation periods. All ocular irritation had resolved by 72 hours after treatment. The mean eye irritation score was 3.2 (range 2-7).

Toxicity Category - III.

V. CLASSIFICATION:

This study does not satisfy the guideline requirements (§81-4) for a primary eye irritation study in rabbits, but it may be upgraded with the submission of the Batch # of the test material used in this study, individual body weight/clinical signs data, and information on whether the test material was ground into a fine powder before testing.

VI. STUDY DEFICIENCIES

There was no information on whether the test material, which was stated to be a white solid, was ground into a fine dust before being introduced into the eyes. Additionally, the Batch # of the test material was not provided, nor were body weight/clinical signs data.